Remarks

The Amendments

Claims 15 and 28 have been amended solely to remove dependencies from non-elected claims. The amendments are not narrowing amendments.

Objection to Claims 15 and 28

Claims 15 and 28 stand as objected to as depending from non-elected claims. Claims 15 and 28 have been amended so that they do not depend from non-elected claims. Applicants respectfully request removal of the objection.

Rejection of Claims 15, 16 and 28 Under 35 U.S.C. §112, first paragraph

Claims 15, 16, and 28 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Applicants respectfully traverse the rejection.

Under 35 U. S. C. § 112, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. §2164.01. "The determination of what constitutes undue experimentation is a given case requires the application of a standard of reasonableness, having due regard of the nature of the invention and the state of the art." *In re Wa*nds, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *Ansul Co. v. Uniroyal, Inc.*, 169 U.S.P.Q. 759, 762-63 (2d Cir. 1971). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it merely routine, or if the specification in question

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provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*

The Office Action asserts that it is possible that a polypeptide identified using IVIAT methodology may not be immunogenic and cites Handfield *et al.* (Trends in Microbiology, 8:336 (2000) at page 337, right column) to support this assertion. However, the paper actually states:

> As in the case of other *in vivo* expression technologies, we are aware that IVIAT is not expected to identify every virulence factor expressed by a particular pathogen. In certain cases it is possible that the product of an *in vivo* expressed gene will not be immunogenic.

In other words, the paper is stating that expressed virulence factors that are not immunogenic will not be detected by IVIAT. Contrary to the Office Action's interpretation, the paper does not state that IVIAT will identify polypeptides that are possibly non-immunogenic.

Furthermore, polypeptides discovered using IVIAT methodology, including polypeptides comprising SEQ ID NO:52, are indeed immunogenic as taught by the specification. The attached declaration of Dr. Handfield describes experiments that clearly demonstrate polypeptides that comprise SEQ ID NO:52 (among other IVIAT polypeptides), are indeed immunogenic. See paragraphs 3-7 of the attached declaration.

The Office Action asserts that it is not clear if false positive reactions would occur with IVIAT-discovered polypeptides due to immunological cross reactivity with other pathogens. Polypeptides identified using IVIAT methodology, including a polypeptide comprising SEQ ID NO:52, do not exhibit non-specific cross reactivity to polypeptides in human sera, nor do they exhibit or cross reactivity to polypeptides from an immune

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response initially raised against other bacterial antigens. *See, e.g.,* paragraphs 3 and 5 of the attached declaration.

The Office Action asserts that the specification lacks support for any and all isolated immunogenic polypeptide fragments that comprise at least 5 contiguous amino acids of SEQ ID NO:52. The specification teaches that SEQ ID NO:52 is an immunogenic polypeptide of the invention. The specification also teaches that polypeptides of the invention comprise:

> biologically functional equivalents of at least about 5, 10, 25, 50, 100, or 200 amino acids of the polypeptides shown in the polypeptide SEQ IDs. A polypeptide is a biological equivalent if it reacts substantially the same as a polypeptide of the invention in an assay such as an immunohistochemical assay, an ELISA, an RIA, or a western blot assay, e.g. has 90-110% of the activity of the original polypeptide. In one embodiment, the assay is a competition assay wherein the biologically equivalent polypeptide is capable of reducing binding of the polypeptide of the invention to a corresponding reactive antigen or antibody by about 80, 95, 99, or 100%. See specification page 13, lines 20 through page 14, line 5.

The specification also teaches polypeptides of the invention comprise an antigen can comprise one or more epitopes (or antigenic determinants). The specification goes on to explain how the epitopes of a polypeptide can be identified using routine methods know in the art. *See e.g.,* page 14, lines 6-21. One of skill in the art could identify polypeptide fragments that are biologically functional equivalents to polypeptides comprising SEQ ID NO:52 using only routine experimentation given the specification, which provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Therefore, one of skill in the art could make and use fragments of SEQ ID NO:52 without undue experimentation.

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The Office Action asserts that SEQ ID NO:52 has not been characterized. However, due to the methodology used to isolate SEQ ID NO:52, much is know about the polypeptide, including that it is an immunogenic, *in vivo* expressed antigen. See specification page 10, line 8 through page 10, line 1; page 24, line 19 through page 25, line 7. The amino acid sequence of the polypeptide is also known. Furthermore, the polypeptide has been characterized in detail as explained in the attached declaration. See paragraphs 3 and 4.

The Office Action asserts that it is not clear if all serotypes of *A. actinomycetemocomitans* during infection could be identified or whether the claimed methods would be able to detect and differentiate all *A. actinomycetemocomitans* strains in a test sample. While not commenting on the capabilities of the claimed methods, Applicants point out that the instant claims do not recite such limitations.

Therefore, one of skill in the art, given the specification, could make and use the methods recited in claims 15, 16, and 28 without undue experimentation. Applicants respectfully request withdrawal of the rejection.

Rejection of Claim 28 Under 35 U.S.C. §102(b)

Claim 28 stands rejected under 35 U.S.C. §102(b) as allegedly anticipated by Flemmig *et al.* Applicants respectfully traverse the rejection.

Under 35 U.S.C. § 102, a claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. *Verdegaal Bros. v. Union Oil Co.*, 2 USPQ2d 1051, 10533 (Fed. Cir. 1987); *In re Recombinant DNA Technology Patent and Contract Litigation*, 30 USPQ2d 1881, 1885 (S.D. Ind.1993) ("A patent is anticipated only if all the elements and limitations of the claims are found within a single, prior art

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reference."); *Structural Rubber Products Co. v. Park Rubber Co.*, 223 USPQ 1264, 1270 (Fed. Cir. 1984) (All elements of the claimed invention must be contained in a single prior art disclosure and must be arranged in the prior art disclosure as in the claimed invention); M.P.E.P § 2131. Furthermore, no difference may exist between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of invention. *In re Recombinant DNA Technology Patent and Contract Litigation*, 30 USPQ2d 1881, 1885 (S.D. Ind.1993). Also, the identical invention must be described or shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); *Chester v. Miller*, 15 USPQ2d 1333 (Fed. Cir. 1990); M.P.E.P. § 2131.

The Office Action asserts that Flemmig teaches the use of outer membrane proteins from *A. actinomycetemocomitans* to detect antibodies specific for *A. actinomycetemocomitans* in patients. The Office Action asserts that the outer membrane proteins taught by Flemmig inherently contain the claimed polypeptides because the outer-membrane proteins were obtained from cell lysates that contain a mixture of polypeptides including a polypeptide comprising SEQ ID NO:52.

However, Flemmig does not teach or suggest an element of the claims, that is, SEQ ID NO:52. Therefore, the Flemmig reference cannot anticipate the claims. The Office Action asserts, however, that a teaching of SEQ ID NO:52 is inherently present in Flemmig.

The fact that a certain characteristic may occur or be present in a prior art reference is not sufficient to establish the inherency of that characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578,

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581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted); MPEP §2112.01. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original); MPEP §2112.01.

The presence of a polypeptide comprising SEQ ID NO:52 does not necessarily flow from the teachings of Flemmig. Flemmig teaches outer membrane proteins of *A. actinomycetemocomitans* that are isolated from ***in vitro* grown cultures**. See Flemmig, page 678, col. 2., third and fourth full paragraphs. Polypeptides of the invention, including SEQ ID NO:52 are not expressed under these *in vitro* growth conditions. The IVIAT methodology, which was used to identify SEQ ID NO:52, specifically removes any antigens that are expressed under *in vitro* growth conditions. The specification teaches that:

> Briefly, IVIAT comprises obtaining a sample of antibodies against Aa antigens that are expressed by Aa *in vivo* and *in vitro* and adsorbing the antibodies with cells or cellular extracts of Aa that have been grown *in vitro*. An example of a sample of antibodies that can be used is sera from patients who have been or are infected with Aa. The unadsorbed

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> antibodies are isolated and are used to probe an expression library of Aa DNA. Reactive clones are isolated and the cloned fragments sequenced.
>
> IVIAT was used to identify polynucleotides of Aa that are expressed only when Aa is engaged in actually causing disease in animals, and in particular humans. Important environmental signals that normally cause Aa to turn on virulence genes during an infection are missing when the bacteria are grown in the laboratory. Therefore, many of the best targets for diagnostic and vaccine strategies were unknown. IVIAT methodology was used to identify polynucleotides that are specifically turned on during growth of Aa in a human host and not during routine laboratory growth. See specification page 9, first and second full paragraphs.

Therefore, a polypeptide comprising SEQ ID NO:52 is not inherently present in Flemmig because the IVIAT methodology used to identify a polypeptide comprising SEQ ID NO:52 specifically identifies polypeptides expressed soley *in vivo* and specifically eliminates selection of polypeptides that are expressed *in vitro* or are expressed *in vivo* and *in vitro*. The proteins used in Flemmig are expressed only *in vitro* or possibly *in vitro* **and** *in vivo* because the cultures used to isolate the proteins were **grown *in vitro***. As such, polypeptides comprising SEQ ID NO:52 are not inherently present in Flemmig. The Office has not provided a basis in fact and/or technical reasoning to reasonably support the determination that the polypeptides comprising SEQ ID NO:52 necessarily flows from the teachings of Flemmig.

Claim 28 is not anticipated by Flemmig and applicants respectfully request withdrawal of the rejection.

Rejection of Claim 28 Under 35 U.S.C. §102(b)

Claim 28 stands rejected under 35 U.S.C. §102(b) as allegedly anticipated by Ebersole *et al.* Applicants respectfully traverse the rejection.

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The Office Action asserts that Ebersole teaches the use of *A. actinomycetemocomitans* outer membrane proteins to detect the presence of antibodies to *A. actinomycetemocomitans*. The Office Action asserts that polypeptides comprising SEQ ID NO:52 would be inherent in the *A. actinomycetemocomitans* outer membrane preparation of Ebersole because the outer membrane proteins were obtained from cell lysates containing a mixture of polypeptides including a polypeptide comprising at least SEQ ID NO:52. The Office Action concludes that a polypeptide comprising SEQ ID NO:52 would be inherent in the outer membrane protein preparation of Ebersole.

However, Ebersole does not teach or suggest an element of the claims, that is, SEQ ID NO:52. Therefore, Ebersole cannot anticipate the claims. The Office Action asserts, however, that a teaching of SEQ ID NO:52 is inherently present in Ebersole.

The presence of a polypeptide comprising SEQ ID NO:52 does not necessarily flow from the teachings of Ebersole. Ebersole teaches outer membrane proteins of *A. actinomycetemocomitans* that are isolated from ***in vitro* grown cultures**. See Ebersole, page 659, second col., first and fourth full paragraphs. Polypeptides of the invention, including SEQ ID NO:52, are not expressed under these *in vitro* growth conditions. The IVIAT methodology, which was used to identify SEQ ID NO:52, specifically removes any antigens that are expressed under *in vitro* growth conditions (see discussion for Flemmig, above).

Therefore, a polypeptide comprising SEQ ID NO:52 is not inherently present in Ebersole because the IVIAT methodology used to identify a polypeptide comprising SEQ ID NO:52 specifically identifies polypeptides expressed only *in vivo* and specifically eliminates selection of polypeptides that are expressed *in vitro* or are expressed *in vivo*

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and *in vitro*. The proteins used in Ebersole are expressed only *in vitro* or possibly *in vitro* **and** *in vivo* because the cultures used to isolate the proteins were **grown *in vitro***. As such, polypeptides comprising SEQ ID NO:52 are not inherently present in Ebersole. The Office has not provided a basis in fact and/or technical reasoning to reasonably support the determination that the polypeptides comprising SEQ ID NO:52 necessarily flows from the teachings of Ebersole.

Claim 28 is not anticipated by Ebersole and applicants respectfully request withdrawal of the rejection.

Rejection of Claims 15-16 Under 35 U.S.C. §102(b)

Claims 15 and 16 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Snyder *et al.* EP 0439210 (Snyder '210); EP 0439211 (Snyder '211); or EP 0439212 (Snyder '212). Applicants respectfully traverse the rejection.

The Office Action asserts that the Snyder references teach the use of polyclonal antibodies specific for *A. actinomycetemocomitans* antigens to detect *A. actinomycetemocomitans*, wherein the *A. actinomycetemocomitans* antigens are expressed *in vivo* during infection of an animal. The Office Actions asserts that the disclosed polyclonal antibodies specifically bind to *A. actinomycetemocomitans* polypeptides comprising SEQ ID NO:52 since the polyclonal antibodies are raised against all *A. actinomycetemocomitans* polypeptides. The Office Action appears to assert that an antibody that specifically binds to a purified immunogenic polypeptide comprising SEQ ID NO:52 would be inherent in the teachings of the Snyder references.

However, the Snyder references do not teach or suggest an element of the claims, that is, an antibody that specifically binds to a purified immunogenic polypeptide

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comprising SEQ ID NO:52. Therefore, the Snyder references cannot anticipate the claims. The Office Action appears to assert, however, that a teaching of an antibody or fragments thereof that specifically binds to a purified immunogenic polypeptide comprising SEQ ID NO:52 is inherently present in the Snyder references.

The presence of an antibody that specifically binds to a purified immunogenic polypeptide comprising SEQ ID NO:52 does not necessarily flow from the teachings of the Snyder references. The Snyder references teach that the polyclonal antibodies used in the disclosed methods are generated by injecting rabbits with whole ***in vitro*** **grown** cultures of *A. actinomycetemocomitans*. See Snyder ('212) page 10, Col. 15, lines 10 through 45; Snyder ('210) page 9, lines 3-49; Snyder ('211) page 3, Col. 3, line 55 through Col. 4, line 24. A polypeptide comprising SEQ ID NO:52 is not expressed under these *in vitro* growth conditions. As such, the antibodies preparations of Snyder would not include antibodies specific for polypeptides comprising SEQ ID NO:52. The IVIAT methodology, which was used to identify SEQ ID NO:52, specifically removes any antigens that are expressed under *in vitro* growth conditions (see discussion for Flemmig, above).

Therefore, an antibody that specifically binds to a purified immunogenic polypeptide comprising SEQ ID NO:52 is not inherently present in the Snyder references because the IVIAT methodology used to identify a polypeptide comprising SEQ ID NO:52 specifically identifies polypeptides expressed only *in vivo* and specifically eliminates selection of polypeptides that are expressed *in vitro* or are expressed *in vivo* and *in vitro*. The antigens used in the Snyder references to immunize rabbits and

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produce polyclonal antibodies are expressed only *in vitro* or possibly *in vitro* **and** *in vivo* because the antigens were ***in vitro*** **grown** cultures of *A. actinomycetemocomitans*.

The Office Action asserts that the *A. actinomycetemocomitans* antigens of the Snyder references are expressed *in vivo* during infection of an animal and cites Snyder ('210) page 1, lines 57-64 and Snyder ('211) page 1, lines 57-63 and Snyder ('212) page 1, left col., lines 5 through right column. No support for this assertion can be found by the applicants at the cited portions of the references. Nonetheless, the Snyder references clearly use antigens that are expressed *in vitro* or possibly *in vitro* **and** *in vivo* to produce their polyclonal antibodies. These polyclonal antibodies would not bind to a purified immunogenic polypeptide comprising SEQ ID NO:52 because a polypeptide comprising SEQ ID NO:52 would not have been present in an *in vitro* culture of *A. actinomycetemocomitans* cells. As such, an antibody or fragments thereof that specifically binds to a purified immunogenic polypeptide comprising SEQ ID NO:52 is not inherently present in the Snyder references. The Office has not provided a basis in fact and/or technical reasoning to reasonably support the determination that a teaching of antibodies or fragments thereof that specifically binds to a purified immunogenic polypeptide comprising SEQ ID NO:52 necessarily flows from the teachings of the Snyder references.

Claims 15 and 16 are not anticipated by the Snyder references and applicants respectfully request withdrawal of the rejection.

Rejection of Claims 15-16 Under 35 U.S.C. §102(b)

Claims 15 and 16 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Snyder *et al.* EP 537830. Applicants respectfully traverse the rejection.

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The Office Action asserts that Snyder anticipates the claims because Snyder teaches an ELISA method for detecting the presence of *A. actinomycetemocomitans* or *A. actinomycetemocomitans* antigens by contacting a test sample with an antibody specific for *A. actinomycetemocomitans*.

Snyder does not teach or suggest an element of the claims, that is, an antibody that specifically binds to a purified immunogenic polypeptide comprising SEQ ID NO:52. Therefore, Snyder cannot anticipate the claims. The Office Action appears to assert, however, that a teaching of an antibody or fragments thereof that specifically binds to a purified immunogenic polypeptide comprising SEQ ID NO:52 is inherently present in Snyder.

The presence of an antibody that specifically binds to a purified immunogenic polypeptide comprising SEQ ID NO:52 does not necessarily flow from the teachings of Snyder. Snyder ('830) is characterized as an improvement over the methods of the Snyder '210 reference discussed above. See page 2, lines 25-37. Snyder ('830) uses the same methods of preparing polyclonal antibodies as disclosed in Snyder '210. See page 5, lines 41-50 and page 8, lines 17-25. Therefore Snyder teaches that the polyclonal antibodies used in the disclosed methods are generated by injecting rabbits with whole ***in vitro*-grown** cultures of *A. actinomycetemocomitans*. See also, Snyder ('210) page 9, lines 3-49. A polypeptide comprising SEQ ID NO:52 is not expressed under these *in vitro* growth conditions. As such, the antibodies preparations of Snyder would not include antibodies specific for polypeptides comprising SEQ ID NO:52. The IVIAT methodology, which was used to identify SEQ ID NO:52, specifically removes any

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antigens that are expressed under *in vitro* growth conditions (see discussion for Flemmig, above).

Therefore, an antibody that specifically binds to a purified immunogenic polypeptide comprising SEQ ID NO:52 is not inherently present in Snyder because the IVIAT methodology used to identify a polypeptide comprising SEQ ID NO:52 specifically identifies polypeptides expressed only *in vivo* and specifically eliminates selection of polypeptides that are expressed *in vitro* or are expressed *in vivo* and *in vitro*. The antigens used in Snyder to immunize rabbits and produce polyclonal antibodies are expressed only *in vitro* or possibly *in vitro* **and** *in vivo* because the antigens were derived from ***in vitro*** **grown** cultures of *A. actinomycetemocomitans*.

The polyclonal antibodies of Snyder would not bind to a purified immunogenic polypeptide comprising SEQ ID NO:52 because a polypeptide comprising SEQ ID NO:52 would not have been present in an *in vitro* culture of *A. actinomycetemocomitans* cells. As such, an antibody or fragments thereof that specifically binds to a purified immunogenic polypeptide comprising SEQ ID NO:52 is not inherently present in Snyder. The Office has not provided a basis in fact and/or technical reasoning to reasonably support the determination that a teaching of antibodies or fragments thereof that specifically binds to a purified immunogenic polypeptide comprising SEQ ID NO:52 necessarily flows from the teachings of Snyder.

Claims 15 and 16 are not anticipated by Snyder and applicants respectfully request withdrawal of the rejection.

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